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(57) Abstract

A process for the preparation of a selectively fluorinated organic compound, which process includes reaction of a precursor of said organic compound, the precursor containing at least one Group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.

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Selectively fluorinated organic compounds

The present invention relates to selectively fluorinated organic compounds and their preparation.

The selective fluorination of organic molecules has received considerable attention because of the profound effect that fluorine can have on the physical, chemical and biological properties of a wide range of substrates. For example, the introduction of a difluoromethylene unit into a molecule is an important target since the CF_2 group is isopolar and isosteric with an ether oxygen and has a steric profile not dramatically different to that of a methylene group. Consequently, effective methods for constructing fluorine containing groups such as fluoromethyl, difluoromethylene or trifluoromethyl from readily available, cheap fluorinating agents are highly desirable and many reagents have been developed in order to meet these targets.

The fluorination of sulfur containing substrates offers an attractive route to fluoromethyl, difluoromethylene or trifluoromethyl containing substrates as many sulfur containing organic compounds are readily available from inexpensive starting materials by well established chemistry. Several methods for the fluorodesulfurization of organic compounds have been devised.

These reactions are generally performed by reacting the appropriate sulfur containing substrate with a combination of a source of electrophilic halogen such as N-bromosuccinimide with a fluoride ion donor such as pyridinium poly(hydrogen fluoride). Thus, fluoromethyl containing substrates may be prepared by treating a phenyl thioglycoside with diethylaminosulfur trifluoride and N-bromosuccinimide. Difluoromethylene containing substrates may be prepared by reacting a 1,3-dithiolane with N-bromosuccinimide and pyridinium poly(hydrogen fluoride) or upon reaction with difluoroiodobenzene. Trifluoromethyl

containing substrates may be prepared by treating an orthothio ester with N-bromosuccinimide and pyridinium poly(hydrogen fluoride). However, many of these reagents suffer from the disadvantages of being difficult to handle, they may be highly toxic and may be expensive.

The fluorination of thiocarbonyl containing substrates offers an attractive route to gem-difluoromethylene compounds as such substrates can readily be prepared from aldehydes or ketones by well established routes.

Only a few methods for the fluorodesulfurization of thiocarbonyl containing substrates are known. These typically involve the synthesis of α,α -difluoroethers from thioesters upon reaction with diethylaminosulfur trifluoride (DAST) or with bromine trifluoride. No extension of these methods to other thiocarbonyl derivatives has been proposed and, in addition, the reagents used are toxic, are difficult to handle and may be expensive.

According to the present invention there is provided a process for the preparation of a selectively fluorinated organic compound, which process includes the reaction of a precursor of the said organic compound, the precursor containing at least one group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.

The group VI containing precursor may be a thiocarbonyl containing substrate.

The group VI containing precursor may be contained in an inert solvent.

Preferably, the inert solvent may be a neutral substance such as acetonitrile and desirably may be a polar solvent such as dichloromethane or chloroform or an acid such as sulfuric acid or trifluoroacetic acid.

The halogenating agent may comprise elemental iodine or bromine or an interhalogen compound. The interhalogen

compound may comprise iodine monochloride or iodine monobromide.

The process according to the present invention may be carried out by passing fluorine gas into the group VI containing precursor in solution in a suitable vessel. Alternatively, a flowing stream of the solution may be contacted with a gaseous flow of fluorine in countercurrent fashion.

The reaction of the process may be carried out at a temperature in the range -60°C to $+150^{\circ}\text{C}$ although a temperature of from -20°C to $+50^{\circ}\text{C}$ is preferred.

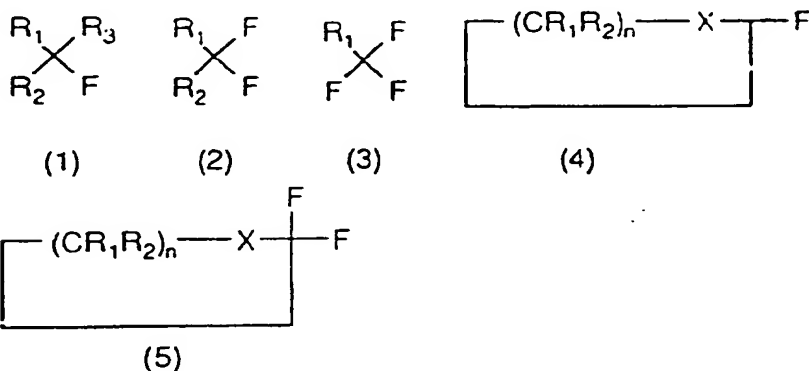
Preferably, the fluorine gas is diluted before use by mixing with an inert gas such as nitrogen or helium. The concentration of fluorine in the inert gas may be from 1% to 50% by volume, preferably from 2% to 25% by volume, and especially from 5% to 15% by volume.

When the fluorination reaction of the process is complete, the selectively fluorinated organic compounds may be isolated by purging the reaction mixture with an inert gas to remove any residual fluorine gas or hydrogen fluoride formed during the reaction, followed by dilution with an excess of aqueous sodium metabisulphite solution and extraction of the selectively fluorinated organic compounds into a suitable solvent followed by purification by distillation or column chromatography.

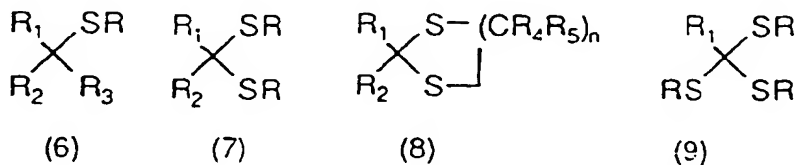
Surprisingly and beneficially the inventors have found that elemental fluorine can be used to convert sulfur containing substrates into corresponding fluoro, difluoro, or trifluoro compounds by relatively simple route using readily available, inexpensive starting materials. In addition, elemental fluorine, when used in conjunction with a halogen such as iodine, permits the difluorination of a wide range of thiocarbonyl derivatives at room temperature in common organic solvents by a process which does not suffer from any of the disadvantages of the methods previously applied to the difluorination of

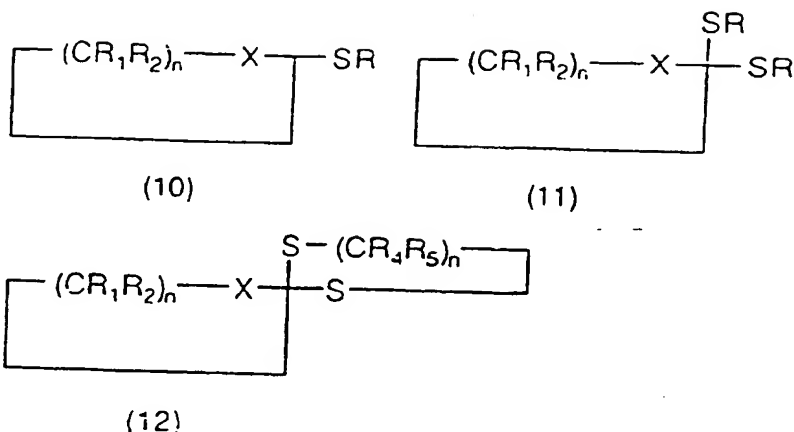
thiocarbonyls. The use of elemental fluorine for the site specific fluorination of organic compounds is rarely satisfactory due to the high reactivity of the element which may cause side reactions. However, in the case of the present invention, the reaction required can be controlled by selection of the rate of fluorine gas applied to the reaction.

The process of the present invention may be used to convert a wide range of compounds containing group VI elements, especially sulfur, to the corresponding fluorinated analogues. In particular, the preparation of fluorine containing compounds of formulae (1), (2), (3), (4) or (5) as follows:



comprises converting the corresponding precursor compounds of formulae (6), (7), (8), (9), (10), (11) or (12) as follows:





into the compounds (1), (2), (3), (4) or (5) by reaction with elemental fluorine as described hereinbefore.

The groups R_1 , R_2 and R_3 may be selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or acetoxy. Where any of the groups R_1 , R_2 or R_3 is an alkyl, cycloalkyl, or aryl substituent, the said group may include one or more optional substituents or hetero atoms.

The groups R , R_4 , and R_5 may be selected from hydrogen, alkyl, cycloalkyl, aryl or substituted aryl.

The substituent X may include oxygen, NH , NR or sulfur.

The structures represented by formulae (4), (5), (8), (10), (11) and (12) are cyclic and n may be an integer in the inclusive range from 1 to 8.

In carrying out the reaction, the ratio of fluorine to compound of formula (6) or (10) may be varied within wide limits although it is preferred that the molar ratio is in

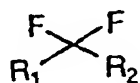
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the range 0.5 to 2.0:1, especially 1.1 to 1.25:1 (fluorine: organic compound). The ratio of fluorine to compound of formula (7), (8), (11) or (12) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (fluorine: organic compound). The ratio of fluorine to compound of formula (9) may be varied within wide limits although it is preferred that the molar ratio is in the range 2.5 to 3.5:1, especially 3.1 to 3.25:1 (fluorine: organic compound).

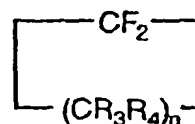
The ratio of halogen or interhalogen to compound of formula (6) or (10) may be varied within wide limits although it is preferred that the molar ratio is in the range 0.5 to 2.0:1, especially 1.1 to 1.25:1 (halogen/interhalogen: organic compound). The ratio of halogen or interhalogen to compound of formula (7), (8), (11), or (12) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (halogen/interhalogen: organic compound). The ratio of halogen or interhalogen to compound of formula (9) may be varied within wide limits although it is preferred that the molar ratio is in the range 2.5 to 3.5:1, especially 3.1 to 3.25:1 (halogen/interhalogen: organic compound).

The process according to the present invention therefore provides an inexpensive and convenient synthetic route to fluorine containing organic compounds.

The process of the present invention may also be used to convert a wide range of thiocarbonyl compounds to the corresponding difluorinated analogues. In particular, the preparation of difluorinated compounds of formulae (13) or (14) as follows:



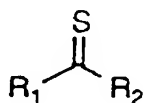
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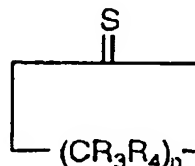
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comprises converting the corresponding thiocarbonyl compounds of formulae (15) or (16) as follows:



(15)



(16)

into the compounds (13) or (14) by reaction with elemental fluorine as described hereinbefore.

The groups R_1 , R_2 , R_3 and R_4 may be selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, perfluoroalkyl, substituted perfluoroalkyl, aryl, substituted aryl or acetoxy. Where any of the groups R_1 , R_2 , R_3 or R_4 is an alkyl, cycloalkyl or aryl substituent, the said group may include one or more optional, substituents or hetero atoms.

The structures represented by formulae (14) and (16) are cyclic and n may be an integer in the inclusive range from 1 to 8.

In carrying out the reaction, the ratio of fluorine to compound of formula (15) or (16) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (fluorine : organic compound).

The ratio of halogen or interhalogen to compound of formula (15) or (16) may be varied between wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (halogen/interhalogen : organic compound).

The process according to the present invention therefore additionally provides an inexpensive and convenient synthetic route to difluoromethene containing organic compounds.

Embodiments of the present invention will now be described, by way of example only, with reference to the following Examples:

Example 1: Preparation of 1-(difluorophenylmethyl)-2,4-dimethylbenzene

A solution 2-phenyl-2-(2',4'-dimethylphenyl)-1,3-dithiolane (2.4g, 8.5mmol), iodine (4.3g, 17mmol) and acetonitrile (40ml) was placed in a PTFE fluorination vessel with attached soda lime filled drying tube. Fluorine gas (17mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at ca 4.0ml/min. The mixture was added to a 10% sodium metabisulfite solution (50ml), extracted with dichloromethane (3x50ml), dried (MgSO₄) and evaporated. Column chromatography on silica gel using 9:1 hexane/ether as the eluant gave pure 1-(difluorophenylmethyl)-2,4-dimethylbenzene which was obtained as a clear liquid in 65% isolated yield: δ H (250MHz, CDCl₃, Me₄Si) 2.15ppm (3H, s, CH₃), 2.31 (3H, s, CH₃), 6.9-7.4 (8H, m, Ar-H); δ F (235MHz, CDCl₃, CFCl₃) -86.7ppm (s); m/z (EI⁺) 232 (M⁺, 100%), 217 (24), 211 (21), 197 (33), 154 (89), 127 (27), 105 (16), 77 (15); as compared to the literature data.

Example 2: Preparation of 1-(difluorophenylmethyl)-4-bromobenzene

In a similar reaction to that described in Example 1, 2-phenyl-2-(4' bromophenyl)-1,3-dithiolane gave 1-(difluorophenylmethyl)-4-bromobenzene as a clear liquid in 61% isolated yield: δ H (250MHz, CDCl₃, Me₄Si) 7.32 - 7.52ppm (m, Ar-H); δ F (235MHz, CDCl₃, CFCl₃) -89.5ppm (s); δ C (100MHz, CDCl₃, Me₄Si) 120.37ppm (t, ¹J 242, CF₂), 124.4 (t, ⁴J 2.3, C-3"), 125.8 (t, ³J 5.7, C-2"), 127.6 (t, ³J 5.5, C-2'), 128.5 (s, C-4"), 130.1 (t, ⁴J 1.9, C-3'), 131.7 (s, C-Br), 136.9 (t, ²J 29, C-1"), 137.3 (t, ²J 28.3, C-1'); m/z (EI⁺) 282 (M⁺, 21%), 284 (M⁺+2, 24), 205 (20), 203 (36), 185 (39), 183 (100), 127(35), 105 (42); as compared to the literature data.

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Example 3: Preparation of 1-(difluoro-4-fluorophenyl-methyl)-4-fluorobenzene

In a similar reaction to that described in Example 1, bis (4'-fluorophenyl)-1,3-dithiolane gave 1-(difluoro-4-fluorophenyl-methyl)-4 fluorobenzene as a clear liquid in 66% isolated yield; δ_H (100MHz, $CDCl_3$, Me_4Si) 7.06ppm (4H, m, Ar-H), 7.45 (4H, m, Ar-H); δ_F (235MHz, $CDCl_3$, CFC_3) - 86.8 (2F, s, CF_2), -111.0 (2F, s Ar-F); δ_C (100MHz, $CDCl_3$, Me_4Si) 115.62 (d, 2J 22.0, C-3), 120.20 (t, 1J 241.8, CF_2), 128.16 (d t, 3J 8.4 and 5.5, C-2), 133.63 (t d, 2J 28.9, 4J 3.4, C-1), 163.74 (d t, 1J 250.2, 5J 2.0, C-4); m/z (EI^+) 240 (M^+ , 100%), 221 (27), 218 (26), 201 (13), 145 (80), 123 (39), 95 (57); as compared to the literature data.

Example 4: Preparation of difluorodiphenylmethane

In a similar reaction to that described in Example 1, benzothiophenone gave difluorodiphenylmethane as a clear liquid in 56% isolated yield; δ_H (250MHz, $CDCl_3$, Me_4Si) 8.43ppm (m, Ar-H); δ_F (235MHz, $CDCl_3$, CFC_3) -89.2ppm (s); m/z (EI^+) 204 (M^+ , 100%), 183 (37), 127 (89), 77 (23); as compared to the literature data.

Example 5: Preparation of 9,9-difluoro-9H-fluorene

In a similar reaction to that described in Example 1, 9H-fluorenyl-1,3-dithiolane gave 9,9-difluoro-9H-fluorene as a white solid in 52% isolated yield; δ_H (250MHz, $CDCl_3$, Me_4Si) 7.35 - 7.7ppm (m, Ar-H); δ_F (235MHz, $CDCl_3$, CFC_3) -112.1ppm; δ_C (100MHz, $CDCl_3$, Me_4Si) 120.35ppm (s, Ar-H), 123.22 (t, 1J 242.6, CF_2), 123.80 (s, Ar-H), 128.76 (s, Ar-H), 132.00 (s, Ar-H), 138.04 (t, 2J 25.1, C-1), 139.50 (t, 3J 5.1, C-2); m/z (EI^+) 202 (M^+ , 55%), 201 (100), 183 (41), 181 (21), as compared to the literature data.

Example 6: Preparation of 1-(difluorophenylmethyl)-4-chlorobenzene

In a similar reaction to that described in Example 1, 2-phenyl-2-(4'-chlorophenyl)-1,3-dithiolane gave 1-

(difluorophenylmethyl-4-chlorobenzene as a clear liquid in 64% isolated yield; δ_H (250MHz, $CDCl_3$, Me_4Si) 7.64 (m, Ar-H); δ_F (235MHz, $CDCl_3$, CFC_3) -89.2ppm (s); m/z (EI^+) 238 (M^+ , 100%), 240 ($M^+ + 2$, 27), 219 (14), 203 (99), 183 (44), 163 (20), 161 (52), 127 (41), 77 (11), as compared to the literature data.

Example 7: Preparation of β -D-glucopyranosyl fluoride tetraacetate

Elemental fluorine gas (3.4mmol diluted to a 10% solution in nitrogen) was bubbled slowly through a mixture of phenyl-1-thio- β -D-glucopyranoside tetraacetate (0.75g, 1.7mmol) and iodine (0.86g, 3.4mmol) in dry acetonitrile (15ml). After the addition of fluorine was complete the solution was poured into 10% sodium metabsulfite and extracted with dichloromethane. The organic layer was washed sequentially with 10% sodium bicarbonate and water, dried ($MgSO_4$) and evaporated to a thick yellow syrup. ^{19}F nmr analysis of the product mixture showed the presence of both anomers with ratio $\alpha:\beta = 1:6$. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure β -D-glucopyranosyl fluoride tetraacetate (320mg, 54%) as white crystals; m.p. 87-88°C from ether [lit. 89°C]; $[\alpha]_D +20.8$ (lit., $[\alpha]_D 20.0$); R_f 0.52; (Found: C, 47.7; H, 5.55. Calc. for $C_{14}H_{19}O_9F$: C, 48.0, H, 5.4%); δ_H (400MHz, $CDCl_3$, Me_4Si) 2.04, 2.05, 2.10, 2.11 (each 3H, s, CH_3 groups), 3.90 (1H, d d d, $J_{4,5} 9.4$, $J_{5,6a} 4.8$, $J_{5,6b} 2.8$, H-5), 4.22 (1H, d d, $J_{6a,6b} 12.4$, $J_{5,6b} 2.8$, H-6b), 4.27 (1H, d d, $J_{6a,6b} 12.4$, $J_{5,6a} 4.4$, H-6a), 5.11 (1H, m, H-2), 5.21 (2H, m, H-3,4), 5.37 (1H, d d, $^1J_{H,F} 52.4$, $J_{H1,H2} 5.4$, H-1); δ_C (100MHz, $CDCl_3$, Me_4Si) 20.6ppm and 20.7 (s, CH_3 groups overlapping), 61.7 (s, C-6), 67.4 (s, C-4), 71.1 (d, $^2J_{C,F} 28.6$, C-2), 71.8 (d, $^3J_{C,F} 8.4$, C-3), 72.0 (d, $^3J_{C,F} 4.2$, C-5), 106.2 (d, $^1J_{C,F} 219.7$, C-1), 169.1, 169.3, 170.0 and 170.6 (s, C=O groups); δ_F (235MHz, $CDCl_3$, Me_4Si) -141.88ppm (d d, $^1J_{H,F} 53.0$, $^2J_{H,F} 12.5$,

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F-1); m/z (Cl^+ , NH_3) 331 (M^+-F , 100%).

Example 8: Preparation of 4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)- β -D-glucopyranosyl fluoride triacetate

In a similar reaction to that described in Example 7, but using phenyl-4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-1-thio- β -D-glucopyranoside triacetate as the starting material, ^{19}F nmr analysis of the crude product mixture obtained showed the presence of both fluoro-anomers with $\alpha:\beta$ ratio 1:10. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (7:3) as eluant yielded pure 4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)- β -D-glucopyranosyl fluoride triacetate (375mg, 57%) as white crystals: R_F 0.62; δ_H (400MHz, $CDCl_3$, Me_4Si) 2.01, 2.03, 2.05, 2.06, 2.10, 2.11 and 2.12 (each 3H, s, CH_3 groups); 3.99 (1H, m, H-5'), 4.01 (1H, m, H-5), 4.08 (1H, d d, $J_{H6a',H6b'}$ 12.4, $J_{H5',H6a'}$ 2.4, H-6a'), 4.16 (1H, t, $J_{H4,H5}$ 8.4, H-4), 4.22 (1H, d d, $J_{H6a,H6b}$ 12.0, $J_{H5,H6b}$ 4.4, H-6b), 4.25 (1H, d d, $J_{H6a',H6b'}$ 12.8, $J_{H5',H6b'}$ 4.0, H-6b'), 4.55 (1H, d d, $J_{H6a,H6b}$ 12.0, $J_{H5,H6a}$ 3.2, H-6a), 4.85 (1H, d d, $J_{H2',H3'}$ 10.8, $J_{H1',H2'}$ 4.0, H-2'), 4.95 (1H, m, H-2), 5.07 (1H, t, $J_{H4',H5'}$ 10.0, H-4'), 5.14 (1H, t, $J_{H3,H4}$ 7.0, H-3), 5.38 (1H, t, $J_{H3',H4'}$ 10.0, H-3'), 5.42 (1H, d, $J_{H1',H2'}$ 4.0, H-1'), 5.43 (1H, d d, $J_{H1,F}$ 52.4, $J_{H1,H2}$ 4.8, H-1); δ_C (100MHz, $CDCl_3$, Me_4Si) 20.56, 20.60, 20.62, 20.69, 20.79, 20.86 (each s, CH_3 groups), 61.49 (s, C-6'), 62.64 (s, C-6), 67.98 (s, C-4'), 68.60 (s, C-5'), 69.29 (s, C-3'), 70.15 (s, C-2'), 71.23 (d, $^2J_{C,F}$ 31.6, C-2), 71.97 (s, C-4), 72.29 (s, C-5), 74.02 (d, $^3J_{C,F}$ 5.3, C-3), 95.90 (s, C-1'), 105.46 (d, $^1J_{C,F}$ 219.7, C-1), 169.36, 169.43, 169.98, 170.04, 170.45, 170.55 (each s, C=O groups); δ_F (376MHz, $CDCl_3$, Me_4Si) -131.9ppm (d d, $^1J_{H,F}$ 52.6, $^2J_{H,F}$ 8.3, F-1); m/z (Cl^+ , NH_3) 656 (M^++18 , 52%).

Example 9: Preparation of α -D-mannopyranosyl fluoride tetraacetate

In a similar reaction to that described in Example 7, but using phenyl-1-thio-D-mannopyranoside tetraacetate as the starting material, ^{19}F nmr analysis of the product mixture obtained showed the presence of only the α anomer. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure α -D-mannopyranosyl fluoride tetraacetate (265mg, 47%) as a clear oil; R_F 0.52; δ_H (400MHz, CDCl_3 , Me_4Si) 2.1, 2.3, 2.6 and 2.9ppm (each 3H, s, CH_3 groups), 4.12-4.20 (2H, m, H-5 and H-6a), 4.30 (1H, d d, $J_{6a,6b}$ 12.8, $J_{5,6b}$ 5.2, H-6b), 5.32-5.36 (2H, m, H-3 and H-4), 5.40 (1H, m, H-2), 5.58 (1H, d d, $J_{H1,F}$ 48.4, $J_{H1,H2}$ 2.0, H-1); δ_F (235MHz, CDCl_3 , CFCl_3) -138.8ppm (d, $J_{H,F}$ 46.4, F-1); δ_C (100MHz, CDCl_3 , Me_4Si) 20.54, 20.60 and 20.67ppm (each s, CH_3 groups), 61.83 (s, C-6), 64.99 (s, C-4), 67.63 (d, $^2J_{C-F}$ 39.3, C-2), 68.13 (s, C-5), 70.85 (d, $^3J_{C-F}$ 3.0, C-3), 104.70 (d, $^1J_{C-F}$ 223.9, C-1), 169.53, 169.62, 169.69 and 170.53 (each s, C=O groups).

Example 10: Preparation of β -D-galactopyranosyl fluoride tetraacetate

In a similar reaction to that described in Example 7, but using phenyl-1-thio- β -D-galactopyranoside tetraacetate as the starting material, ^{19}F nmr analysis of the product mixture obtained showed the presence of only α and β anomers in ratio $\alpha:\beta$ 1:7. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure β -D-galactopyranosyl fluoride tetraacetate (300mg, 51%) as a clear oil; R_F 0.45; δ_H (400MHz, CDCl_3 , Me_4Si) 4.06 (1H, t, $J_{5,6}$ 6.4, H-5), 4.21 (2H, d d, $J_{5,6}$ 6.6, $J_{6a,6b}$ 1.6, H-6), 5.05 (1H, d d, $J_{2,3}$ 10.4, $J_{3,4}$ 3.2, H-3), 5.26 (1H, d d, $J_{H,F}$ 54.0, $J_{1,2}$ 7.2, H-1), 5.42 (1H, m, H-4), 5.31 (1H, m, H-2); δ_F (235MHz, CDCl_3 , CFCl_3) -143.11ppm (d d, $J_{H,F}$ 54.0, $J_{H,F}$ 12.0); δ_C (100MHz, CDCl_3 , Me_4Si) 20.53, 20.60 and

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20.67ppm (each s, CH₃ groups), 61.29 (s, C-6), 66.37 (s, C-4), 68.75 (d, ²J_{C-F} 24.8, C-2), 69.89 (d, ³J_{C-F} 10.7, C-3), 71.17 (d, ³J_{C-F} 4.5, C-5), 107.08 (d, ¹J_{C-F} 218.6, C-1).

Claims

1. A process for the preparation of a selectively fluorinated organic compound, which process includes the reaction of a precursor of the said organic compound, the precursor containing at least one Group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.
2. A process as in Claim 1 and wherein the Group VI containing precursor is a thiocarbonyl containing substrate.
3. A process as in Claim 1 or Claim 2 and wherein the Group VI containing precursor is contained in an inert solvent.
4. A process as in any one of the preceding claims and wherein the halogenating agent comprises elemental iodine or bromine or an interhalogen compound comprising iodine monochloride or iodine monobromide.
5. A process as in any one of the preceding Claims and wherein the reaction is carried out at a temperature in the range -60°C to $+150^{\circ}\text{C}$.
6. A process as in any one of the preceding Claims and wherein the fluorine gas is diluted before use by mixing with an inert gas such that the concentration of fluorine in the inert gas is from 1% to 50% by volume.
7. A process for the preparation of fluorine containing molecules of formulae (1), (2), (3), (4) or (5) as hereinbefore defined, comprising converting the corresponding sulfur containing precursor compounds of formulae (6), (7), (8), (9), (10), (11) or (12) as hereinbefore defined, into the compounds (1), (2), (3), (4) or (5) by reaction with elemental fluorine by the process according to any one of the preceding Claims.
8. A process for the preparation of difluorinated compounds of formulae (13) or (14) as hereinbefore

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defined, comprising converting the corresponding thiocarbonyl compounds of formulae (15) or (16) as hereinbefore defined, into the compounds (13) or (14) by reaction with elemental fluorine by the process according to any one of Claims 1 to 6.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, vol. 2, 1995 LETCHWORTH GB, page 177 R.D. CHAMBERS ET AL. 'The Conversion of Diaryl-1,3-Dithiolanes into gem-Difluoromethylene Compounds by a Combination of Elemental Fluorine and Iodine' see the whole document --- -/--	1-8

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/GB 95/01765

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SYNLETT, no. 3, 1991 STUTTGART DE, pages 191-192, W.B. MOTHERWELL ET AL. 'Observations on the Reaction of Dithioketals with para-Iodotoluene Difluoride: A Novel Route to gem-Difluoro Compounds' see the whole document ---	1,7,8
A	JOURNAL OF ORGANIC CHEMISTRY, vol. 51, 1986 EASTON US, pages 3508-3513, S.C. SONDEJ ET AL. 'gem-Difluoro Compounds: A Convenient Preparation from Ketones and Aldehydes by Halogen Fluoride Treatment of 1,3-Dithiolanes' see the whole document -----	1,7,8